



BLOOD AND MARROW
TRANSPLANT
CLINICAL TRIALS NETWORK

TECHNICAL MANUAL OF PROCEDURES

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TABLE OF CONTENTS

1.	ACUTE GRAFT-VS-HOST DISEASE (GVHD).....	1-1
1.1.	Introduction.....	1-1
1.2.	Mission Statement.....	1-1
1.3.	Acute GVHD Staging and Grading	1-1
1.3.1.	Records	1-1
1.3.2.	Conclusions.....	1-1
1.3.3.	Grading	1-1
1.4.	Data Collection	1-4
1.5.	Chronic GVHD Syndrome.....	1-4
1.6.	Other Staging Schema.....	1-5
1.7.	Pathology Review	1-5
2.	CHRONIC GRAFT-VS-HOST DISEASE (GVHD).....	2-1
2.1.	Introduction.....	2-1
2.2.	Mission Statement.....	2-1
2.3.	Definitions of Chronic GVHD.....	2-1
2.4.	Data Collection	2-2
2.5.	Standards of Care.....	2-2
2.6.	Pediatric Considerations	2-3
2.7.	Evaluation Procedures	2-3
2.8.	Data Audits	2-3
3.	GRAFT CHARACTERIZATION AND PROCESSING FOR HEMATOPOIETIC CELLULAR PRODUCTS	3-1
3.1.	Mission Statement.....	3-1
3.2.	Alignment with Existing Guidelines.....	3-1
3.3.	Record Keeping and Audits.....	3-2
3.4.	Graft Characterization.....	3-3
3.4.1.	Receipt and Labeling	3-3
3.4.2.	Cellular Product Processing and Assays.....	3-3
3.5.	Storage of Research Aliquots.....	3-4
3.6.	Disposal of Unused Cellular Products	3-4
4.	INFECTIOUS DISEASE.....	4-1
4.1.	Introduction.....	4-1
4.2.	Purpose.....	4-1

4.3. Membership 4-1

4.4. Policy 4-1

5. SPECIAL POPULATIONS (PREVIOUSLY PEDIATRIC/HUMAN SUBJECTS) 5-1

5.1. Introduction..... 5-1

5.2. Purpose..... 5-1

5.3. Membership 5-1

5.4. Policy 5-1

6. PHARMACY..... 6-1

6.1. Introduction..... 6-1

6.2. Purpose..... 6-1

6.3. Membership 6-1

6.4. Policy 6-1

7. TOXICITY AND SUPPORTIVE CARE..... 7-1

7.1. Introduction..... 7-1

7.2. Purpose..... 7-1

7.3. Membership 7-1

7.4. Policy 7-1

8. CLINICAL RESEARCH ASSOCIATES 8-1

8.1. Introduction..... 8-1

8.2. Purpose..... 8-1

8.3. Membership 8-1

8.4. Policy 8-1

LIST OF APPENDICES

Appendix 2-A Chronic GVHD

Appendix 2-B Draft Grid for Chronic GVHD Severity Scoring

Appendix 2-C Chronic GVHD Code Book

Appendix 2-D Chronic GVHD Auditing Tool

Appendix 4-A Severity Grading Table and Recurrence Interval Definitions

1. ACUTE GRAFT-VS-HOST DISEASE (GVHD)

1.1. Introduction

The Acute GVHD Technical Committee has reviewed and recommends the following procedures for GVHD evaluation, data collection, scoring, and final acute GVHD severity evaluation for clinical trials performed through the Network.

1.2. Mission Statement

The purpose of the Acute GVHD Technical Committee is to define data collection, grading schemes, and study requirements for pathologic confirmation.

1.3. Acute GVHD Staging and Grading

1.3.1. Records

Investigators should document on a weekly basis (beginning with the day of transplant) the raw data for the GVHD target organs either in the medical record directly or on a trial-specific worksheet (Figure 1.3.1 or Figure 1.3.2). This should include the extent of skin rash, if any; the bilirubin; the daily stool output; or number of stools per day for an outpatient. The weekly record should reflect the worst representative days of the preceding week for each target organ involvement. Biopsy confirmation of target organs is recommended in most circumstances to confirm the diagnosis acute GVHD.

In addition to the raw data record to verify acute GVHD organs staging, the relevant differential diagnoses should be recorded (e.g., drug rash, GI infection such as *C. difficile*, veno-occlusive disease (VOD), total parenteral nutrition (TPN), etc.) each week for target organ involvement. The record should indicate whether a biopsy was diagnostic, not diagnostic, or not done of each organ involved and should indicate when systemic GVHD therapy was initiated.

1.3.2. Conclusions

Each center's conclusion about GVHD involved in the organ (yes/no) and biopsy information, the final maximum GVHD grade and organ stage decided at the center should be collected and used for comparison with any grading algorithm.

1.3.3. Grading

Acute GVHD grading should be performed by the consensus conference criteria (Przepiorka, et. al., 1994) and, for some studies, the Center for International Blood and Marrow Transplant Research (CIBMTR) ABCD grading scheme could be used as well (Rowlings, et. al., 1997). See Tables 1.3.1, 1.3.2 and 1.3.3.

SAMPLE DATA SHEETS (to be adapted to Network data collection methods)

Date of Report	Submit weekly x 8 then at monthly interval while on GVHD therapy													
Name/Study ID #														
	Record Stage & biopsy info when performed or clinical change:													Final Max
AGVHD Grade Record	1= biopsy pos/0= biopsy neg/ 2= biopsy not done eg 22 = stage 2, no biopsy Record Diff. Diagnosis, if any													GVHD grade
	-10 to -7	-6 to -3	-2 to 0	1 to 3	4 to 7	8 to 10	11 to 14	15 to 17	18 to 21	22 to 24	25 to 28	29 to 31	32 to 35	36 to 38
Record Max Grade for this interval														
Skin stage														
GI diarrhea														
Upper GI N/V														
Liver														
Differential Diagnosis														
Drug														
specify														
Infection														
specify														
TPN														
Chemo,XRT														
VOD														
Other														
GVHD therapy 0=none; 1=continue; 2=start														
CSA														
FK506														
Topical Steroids														
Prednisone														
ATG														
Other (specify)														

Figure 1.3.1 – Sample Data Sheet

Clinical Acute GVHD Assessment													
Date _____		Patient ID _____				Karnofsky/Lansky _____							
Code						Differential Diagnosis							
	0	1	2	3	4	5	GVHD	Drug Rxn	Cond Reg	TPN	Infect	VOD	Other
Skin	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	% body rash: _____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	_____
Lower GI	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Vol: _____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	_____
Upper GI	<input type="checkbox"/>	<input type="checkbox"/>						<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	_____
Liver	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Max bili: _____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	_____
Treatment:		<input type="checkbox"/> CSA	<input type="checkbox"/> Tacrolimus	<input type="checkbox"/> Pred	<input type="checkbox"/> Methylpred	<input type="checkbox"/> Ontak							
		<input type="checkbox"/> Pentostatin	<input type="checkbox"/> MMF	<input type="checkbox"/> Etanercept	<input type="checkbox"/> Other _____								
Code Definitions:													
<u>Skin:</u>			<u>Lower GI (Diarrhea):</u>				<u>Upper GI:</u>			<u>Liver (Bilirubin):</u>			
0 No rash			0 None				0 No protracted nausea and vomiting			0 <2.0 mg/dl			
1 Maculopapular rash, <25% of body surface			1 ≤500 mL/day or <280 mL/m ²				1 Persistent nausea, vomiting or anorexia			1 2.1-3.0 mg/dl			
2 Maculopapular rash, 25-50% of body surface			2 501-1000 mL/day or 280- 555 mL/m ²							2 3.1-6.0 mg/dl			
3 Generalized erythroderma			3 1001-1500 mL/day or 556- 833 mL/m ²							3 6.1-15.0 mg/dl			
4 Generalized erythroderma with bullous formation and desquamation			4 >1500 mL/day or >833 mL/m ²							4 >15.1 mg/dl			
			5 Severe abdominal pain with or without ileus, or stool with frank blood or melena										
Signature _____													

Figure 1.3.2 – Clinical Acute GVHD Assessment

TABLE 1.3.1 – GVHD STAGING

Stage	Skin	GI	Liver
1	< 25% rash	Diarrhea > 500ml/d or persistent nausea	Bilirubin 2-3mg/dl
2	25-50%	> 1000 ml/d	Bilirubin 3-6 mg/dl
3	> 50%	> 1500 ml/d	Bilirubin 6-15 mg/dl
4	Generalized erythroderma with bullae	Large volume diarrhea and severe abdominal pain ± ileus	Bilirubin > 15 mg/dl

TABLE 1.3.2 – CONSENSUS GVHD GRADING (PRZEPIORKA, ET. AL., 1995)

Grade	Skin	GI	Liver
I	Stage 1-2	0	0
II	Stage 3 or	Stage 1 or	Stage 1
III	---	Stage 2-4	Stage 2-3
IV	Stage 4	---	Stage 4

TABLE 1.3.3 – CIBMTR GVHD INDEX (ROWLINGS, ET. AL., 1997)

Stage	Skin	GI	Liver
A	Stage 1	0	0
B	Stage 0-2 or	0-2 or	0-2
C	Stage 3 or	3 or	3
D	Stage 4 or	4 or	4

1.4. Data Collection

Weekly GVHD raw data, staging, and grading should be collected until 60-70 days post-transplant for all patients and, if feasible, to Day +100. Subsequently, monthly data involving acute GVHD symptomatology should be collected for all patients remaining on immunosuppressive therapy until two months after discontinuation of immunosuppressive treatment for acute GVHD. If acute GVHD develops later or flares, the data collection should be continued frequently (every 1, 2, or 4 weeks as feasible) in sufficient detail to monitor the progress of the disease.

1.5. Chronic GVHD Syndrome

Late GVHD is a specific syndrome involving, for example, scleroderma, dry eyes, dry mouth, lichenoid oral changes, bronchiolitis obliterans, vanishing bile ducts, and weight loss. It is to be diagnosed specifically rather than diagnosed when acute GVHD-like syndromes develop late (beyond Day +100) after any transplant or donor lymphocyte infusion (DLI).

1.6. Other Staging Schema

Sufficient clinical information is not available or published to distinguish any differences in acute GVHD patterns following non-myeloablative transplants, cord blood transplants, or after DLI. In these settings, acute GVHD organ involvement staging and grading should follow the same plan described above, unless subsequent re-evaluation documents the need for alternative staging and grading schema.

1.7. Pathology Review

The BMT CTN GVHD Technical Committee has developed and commissioned a plan endorsed by the Steering Committee and coordinated with the Pathology Working Committee of the Chronic GVHD Consensus Project (see Appendix 2-A) for a pathology review project to reassess the validity and reproducibility of acute GVHD histologic diagnoses.

Other Organ Evaluation: In addition, involvement of the lung in acute or chronic GVHD requires further definition and study and may be an appropriate topic for prospective evaluation relating to the biology of lung dysfunction after hematopoietic cell transplantation (HCT).

2. CHRONIC GRAFT-VS-HOST DISEASE (GVHD)

2.1. Introduction

In this chapter, definitions of chronic GVHD, guidelines for diagnosis and severity grading, and data collection procedures for allogeneic BMT CTN protocols are provided. The Chronic GVHD Technical Committee will revise this chapter periodically, as new knowledge is gained and therapeutic practices evolve.

For each individual BMT CTN protocol, more or less information regarding chronic GVHD may be required. The Chronic GVHD Technical Committee will provide advice to the Principal Investigator (PI) of each protocol as to the frequency and detail with which chronic GVHD severity should be assessed. It is recognized that the definitions and severity grading described below are not yet validated, but are offered as one consensus of current practice that may be used now pending further methodologic studies.

2.2. Mission Statement

The purpose of the Chronic GVHD Technical Committee is to define methods for evaluation, scoring and grading of chronic GVHD; define study requirements for pathologic confirmation or pathologic review of GVHD diagnostic specimens; devise and approve methods and forms for collection of GVHD related data; determine techniques for verifying GVHD endpoints; and, review multicenter data.

2.3. Definitions of Chronic GVHD

The diagnosis of chronic GVHD is based on both clinical and histopathologic findings for each organ system. Pathognomonic and possible manifestations of chronic GVHD are outlined below; possible manifestations should be further evaluated to rule out other potential non-chronic GVHD etiologies. For example, pancreatic enzyme insufficiency may cause malabsorption and weight loss independent of chronic GVHD.

Time since transplant will not be used to distinguish acute from chronic GVHD (e.g., chronic GVHD may occur before Day 100, and acute GVHD may occur after Day 100). If acute GVHD is suspected after Day 60 or chronic GVHD is suspected before Day 100, biopsies are strongly encouraged to confirm the diagnosis. Additionally, biopsies are encouraged to confirm the diagnosis of chronic GVHD in patients with “possible” manifestations (see Table 2.3.1).

Table 2.3.1 – Definite and Possible Manifestations of Chronic GVHD

Organ System	Definite manifestations of chronic GVHD	Possible manifestations of chronic GVHD
Skin	Scleroderma (superficial or fasciitis), lichen planus, vitiligo, scarring alopecia, hyperkeratosis pilaris, contractures from skin immobility, nail bed dysplasia	Eczematoid rash, dry skin, maculopapular rash, hyperpigmentation, hair loss
Mucous membranes	Lichen planus, non-infectious ulcers, corneal erosions/non-infectious conjunctivitis	Xerostomia, keratoconjunctivitis sicca
GI tract	Esophageal strictures, steatorrhea	Anorexia, malabsorption, weight loss, diarrhea, abdominal pain
Liver	None	Elevation of alkaline phosphatase, transaminitis, cholangitis, hyperbilirubinemia
GU	Vaginal stricture, lichen planus	Non-infectious vaginitis, vaginal atrophy
Musculoskeletal/ Serosa	Non-septic arthritis, myositis, myasthenia, polyserositis, contractures from joint immobilization	Arthralgia
Hematologic	None	Thrombocytopenia, eosinophilia, autoimmune cytopenias
Lung	Bronchiolitis obliterans	Bronchiolitis obliterans with organizing pneumonia, interstitial pneumonitis

The severity of chronic GVHD is difficult to quantify. However, a grid for capturing severity has been proposed and is undergoing testing. The draft grid is provided in Appendix 2-B, and the Committee recommends that trials with chronic GVHD as a primary endpoint use this format until further data are available.

2.4. Data Collection

As noted above, the detail to which chronic GVHD will be monitored and graded will vary from trial to trial and will be stated in advance by the PI for that protocol. For some studies, medical photographs may be useful to record severity and response to treatment. Case report forms are in the BMT CTN Data Management Handbook and User's Guide. The chronic GVHD Code Book is in Appendix 2-C. The Chronic GVHD Technical Committee recommends that these forms be used at present, and they will be modified as data are gathered.

2.5. Standards of Care

Treatment of chronic GVHD and supportive care measures will follow standard local practice, unless otherwise specified by a BMT CTN protocol. Several infectious disease guidelines specifically for patients with chronic GVHD may be found in the guidelines for preventing opportunistic infections developed by the American Society of Blood and Marrow Transplantation, Centers for Disease Control, and Infectious Disease Society of America, published as a supplement to *Biology of Blood and Marrow Transplantation* (6a:659-734, 2000) and posted on the CDC website at www.cdc.gov.

PIs of specific BMT CTN protocols should estimate what, if any, variations in medical management of chronic GVHD might potentially confound their primary or secondary outcomes. If there are serious concerns that practice variation might confound interpretation of endpoints, the Chronic GVHD Technical Committee will assist the PI in determining what data will be necessary to monitor such practices or will provide recommendations for standardization of those practices such that they may be collected prospectively. During the Concept Development process, analyses should be performed to examine potential variables that may have an independent impact on the outcomes in question. If variables are not identified, adjustments may not be required. If variables are identified, a plan to accommodate or adjust for these effects should be incorporated into the analysis plan.

2.6. Pediatric Considerations

Children with chronic GVHD can present with skin, liver, GI, eye, or systemic disease leading to failure to thrive, persistent immunodeficiency, or chronic pulmonary disease. Chronic "eczema" or dry skin are common manifestations of mild chronic GVHD of skin. Liver disease can present as asymptomatic hyperbilirubinemia or elevated alkaline phosphatase. As children can have marked elevations in alkaline phosphatase during growth spurts, children with this laboratory abnormality, a fractionated alkaline phosphatase should be obtained to confirm that the band is from liver and not from bone before a diagnosis of chronic GVHD is made. Children with chronic GVHD of the upper GI tract may have chronic anorexia or poor growth due to malabsorption. Rather than losing weight, children may 'fall off' their growth curve with decreased gains in height or weight velocity. In children < 2 years of age, this may also affect growth of head circumference. Chronic GVHD may also cause persistent low or intermediate grade immunodeficiency. In addition to increasing the risk of opportunistic infection, this may cause GI dysfunction and lead to malabsorption, low IgG (due to protein losing enteropathy), lactose deficiency, and poor growth. Duodenal intubation with quantitation of pancreatic enzymes is useful in these children. If pancreatic enzymes are low, children may benefit from supplementation of pancreatic enzymes.

2.7. Evaluation Procedures

No specific recommendations for frequency of follow-up will be specified for chronic GVHD diagnosis or management across BMT CTN trials, other than that required by good medical practice and completion of the research forms. Protocols with chronic GVHD as a primary or secondary endpoint should specify the frequency and methods of evaluation.

2.8. Data Audits

Auditing will take place in accordance with BMT CTN guidelines. The auditing tool provided in Appendix 2-D provides the template for chronic GVHD variables to be audited. For BMT CTN studies in which chronic GVHD is the primary or major secondary endpoint, centralized pathologic review is encouraged.

3. GRAFT CHARACTERIZATION AND PROCESSING FOR HEMATOPOIETIC CELLULAR PRODUCTS

3.1. Mission Statement

The purpose of the Graft Characterization Technical Committee is to provide guidelines for assessing a hematopoietic cellular product that is to be infused into a patient as part of a BMT CTN clinical trial. This includes record keeping, receipt and labeling, assays, storage of research aliquots and disposal of unused products.

3.2. Alignment with Existing Guidelines

1. Where possible, this procedure defers to established guidelines or standards that relate to the processes discussed herein. Graft processing and characterization for BMT CTN clinical trials are to be performed in accordance with the standards established by FACT, The Foundation for the Accreditation of Cellular Therapy, cGMP and GTP guidelines relating to human tissue intended for transplantation (21 CFR parts 1270 & 1271) and general biologic products standards (21 CFR part 610).
 - The laboratory/medical director provides documented evidence of yearly review of FACT Standards, and 21 CFR parts 610, 1270 and 1271.
2. As BMT CTN core centers are either FACT approved or in the process of obtaining FACT accreditation, where possible, this procedure defers to institutional SOPs for processing, storage and characterization of hematopoietic cellular grafts that are to be infused as part of BMT CTN clinical trials. If affiliate centers that participate in specific trials are not FACT accredited or applied, additional review of their relevant SOPs may be undertaken by the Graft Characterization Technical Committee.
 - The laboratory of a Core Center provides documented evidence that it has attained FACT or American Association of Blood Banks accreditation (date/term), and the following SOPs are reviewed and conform to committee requirements
 - Cryopreservation of human hematopoietic cells for infusion by rate-controlled freezing
 - Labeling of research aliquots
 - The laboratory of an affiliate center provides documented evidence that it has attained FACT or American Association of Blood Banks accreditation (date/term). Alternatively, an SOP matrix has been provided and reviewed and found to be acceptable by the Graft Characterization Technical Committee. At a minimum, the SOP supplied by the center should map to the following general topics:
 - Preparation of cells human hematopoietic cells for cryopreservation
 - Cryopreservation of human hematopoietic cells for infusion by rate-controlled freezing
 - Storage of human hematopoietic cells for infusion
 - Labeling of human hematopoietic cells for infusion

- Labeling of research aliquots (procedure to be determined by committee)
- Analysis of human hematopoietic cells: The specific SOPs that map to this category are defined by the Committee and include:
 - ABO/RH determination,
 - Trypan blue viability determination (or an equivalent approved by the Committee),
 - White blood cell count determination,
 - CD3, CD4, CD8, CD19 and CD56 analysis for allogeneic products
 - CD34 analysis using the ISHAGE method, or validated equivalent, for allogeneic and autologous products
- Sterility testing according to 21 CFR 610.12 or a validated equivalent test
- Review of the patient chart/laboratory worksheets intended to be used during routine graft manipulations for products included in this study determines that
 - Supplies, reagents, equipment and assay results are clearly recorded
 - Allogeneic graft RBC volume is < 20 ml
 - Allogeneic graft ABO/Rh matches Recipient ABO/Rh or manipulation is documented
 - Label verification by double-check are documented
 - Written informed consent has been attained for this study
- Deviation reporting and follow up

3.3. Record Keeping and Audits

- 1) All product testing and manipulations, whether conducted in the BMT Lab or at other sites, are to become part of the patient record. Process documentation shall include: lot numbers of reagents and supplies, identifiers for equipment used, assay results and reports of deviations from standard procedures.
- 2) Local records and SOPs will be reviewed during site audits.
 - Review of the patient chart/laboratory worksheets intended to be used during routine graft manipulations including:
 - Supplies, reagents, equipment and assay results are clearly recorded
 - Allogeneic graft RBC volume is < 20 ml
 - Allogeneic graft ABO/Rh matches Recipient ABO/Rh or manipulation is documented
 - Double checking of label verification is documented

- Review of the laboratory deviation files is consistent with the expectations detailed in the laboratory deviation SOP

3.4. Graft Characterization

All autologous and allogeneic products for transplantation received by the BMT Lab are to be characterized by the assays described herein in order to determine the quality of the product prior to infusion and to assess the efficacy and consistency of product manipulations in preparation for infusion. Assays not applicable to all grafts include descriptions of products to be tested. Additional requirements may be required for certain types of hematopoietic cellular products (e.g. cord blood). When the additional guidelines are required, they will be specified in the trial protocol.

3.4.1. Receipt and Labeling

1. All graft processing is to be done within sterile laminar flow biosafety cabinets using sterile technique. Follow Universal Safety Precautions at all times even if infectious disease testing does not indicate the presence of blood-borne pathogenic agents.
2. Upon receipt of the product, prepare documentation for product labeling. All documentation including labeling and calculations should be verified by a second technologist and will be performed according to FACT approved procedures.

3.4.2. Cellular Product Processing and Assays

1. Refer to institutional SOP for processing. Gently agitate the product to ensure a uniform suspension of cells within the product and remove a sufficient volume of the product to perform the appropriate assays for that product. For products undergoing more than minimal manipulation, pre and post-processing sampling is required.
2. Type the product to determine ABO and Rh blood grouping. The product type must match the patient or donor type on record with Transfusion Service.
3. Determine the hematocrit of the product. Allogeneic donor graft incompatible by ABO and Rh typing shall be manipulated to reduce RBC content to less than 20 ml, as indicated by hematocrit, prior to infusion.
4. Determine the total nucleated cell count (WBC/ml) using either hemacytometer or particle counter cell counts.
5. Determine cell viability differential cell staining according to institutional SOP. Viability should be performed utilizing trypan blue exclusion unless utilizing an alternative viability assay approved by the BMT CTN Graft Characterization Technical Committee. When the scientific question of the protocol relates to graft manipulation or a comparison of graft types etc. more specific viability assay requirements will be contained in the protocol.
6. Determine the hematopoietic stem cell content of the product using CD34 expression as detected by flow cytometry to identify stem cells within the WBC component of the product. Analysis of list mode data is to be in accordance with the ISHAGE guidelines (Sutherland et al., 1996). Non-viable cells are excluded from the analysis by co-staining

with 7-AAD or Propidium Iodide. If a participating center is not utilizing this methodology, the SOP to be used will be reviewed by the Graft Characterization Technical Committee. If the Committee deems necessary, the site will have to participate in a validation process using shared spiked samples for confirmation of their CD34 enumeration methodology.

7. Determine the lymphocyte content including T cells, B cells and NK cells of allogeneic donor products using CD3, CD4, CD8, CD19 and CD56 expression as detected by flow cytometry. Autologous grafts require CD34 enumeration at a minimum.
8. Initiate testing for product sterility using Fluid Thioglycollate and Soybean - Casein Digest media in accordance with 21 CFR 610.12 or a validated equivalent test.

3.5. Storage of Research Aliquots

1. It is strongly recommended for marrow and peripheral bloods stem cell products that five vials of between $2-5 \times 10^6$ nucleated cells be obtained for the central repository. The cells should be cryopreserved to maintain viability and that adequate graft characteristics are obtained according to specific protocol guidelines. These will be shipped at defined periods of time to the central repository. For cord blood transplants, methods for acquiring cells will be described in the protocols.
2. Specimens should be labeled as specified in the BMT CTN protocol.
3. Each center will be required to have a specific consent form or contain in their general consent form, the accepted local institutional IRB language regarding storage of human tissue for future studies.
4. Centers should follow controlled-rate freezing SOPs for cryopreserving research samples as for product storage.

3.6. Disposal of Unused Cellular Products

Disposal of cell products should be performed according to institutional guidelines.

4. INFECTIOUS DISEASE

4.1. Introduction

It is well recognized that infections of all types are common complications in the setting of hematopoietic stem cell transplantation (HCT). Because all or most study participants in BMT CTN trials will be receiving therapies resulting in substantial immunosuppression, frequent occurrences of infectious diseases are anticipated in Network trials.

More or less information regarding infectious complications may be required for each individual BMT CTN protocol. Not all infections and infectious disease practices need be monitored to the same detail. The information herein is offered as suggested guidelines for protocol development.

The Infectious Disease Technical Committee is an ad hoc committee that convenes when necessary for advising Protocol Teams, reviewing infectious disease data, refreshing relevant Manual of Procedures text, etc.

4.2. Purpose

The purpose of the Infectious Disease Technical Committee is to:

- Recommend data collection procedures,
- Define standards for prevention and treatment of infections for both allogeneic and autologous transplantation,
- Provide guidelines for clinical and laboratory monitoring of infections, and
- Define infectious complications and auditing practices.

4.3. Membership

This committee consists of transplant physicians and infectious disease specialists all with substantial experience in HCT. A DCC co-PI serves on the committee in an ex-officio capacity. There is a core group of interested, experienced investigators who are committed to the work of the Network and who convene upon request of a Protocol Team and/or the DCC.

4.4. Policy

The suggested detail to which infectious complications will be monitored varies from trial to trial and will be made in advance by the Protocol Team.

The Protocol Team determines what, if any, variations in medical practice of infection therapy might potentially confound their primary or secondary outcomes. If there are concerns on the part of the Protocol Team, Steering Committee or the Infectious Disease Technical Committee that confounding may occur, the Infectious Disease Technical Committee will assist the Protocol Team in determining what data are necessary to monitor such practices, or the Committee will provide recommendations for standardization of those practices such that they may be collected prospectively.

Procedure: *Recommend data collection procedures*

As a matter of routine, Grade 2 and 3 infections are reported; Grade 1 infections are not reported. A standardized Infection Case Report Form (CRF) is used for all protocols unless Grade 1 reporting is important to the trial endpoint. In this case, a protocol-specific Case Report Form is designed by the Protocol Team. This approach is also consistent with NIH requirements for collecting Severe Adverse Event (SAE) data.

Data auditing will take place in accordance with BMT CTN guidelines.

Procedure: *Define standards for prevention and treatment of infections for both allogeneic and autologous transplantation*

Joint guidelines for preventing opportunistic infections were developed and published as a supplement to *Biology of Blood and Marrow Transplantation* (15: 1143-1238, 2009) and are posted on the CDC website at www.cdc.gov. These are currently used for Network trials, except as specifically modified for particular protocols.

Procedure: *Provide guidelines for clinical and laboratory monitoring of infections*

No specific recommendations for routine infection monitoring are made for primary or secondary endpoint infectious complications. If there are questions, Protocol Teams are encouraged to consult the Infectious Disease Technical Committee as the Committee can assist in developing a timeline schedule of specific clinical and laboratory evaluations.

Procedure: *Define infectious complications*

“BMT CTN Severity Grades by Infection Type” (Attachment 4-A) defines symptomatology associated with bacterial, fungal, viral, parasitic and non-microbiologically. Grades 1 (“mild”, generally not reported), 2 (“moderate”) and 3 (“severe/life threatening”) infections are specifically noted.

Guidelines for infection recurrence intervals are also defined in Attachment 4-A.

5. SPECIAL POPULATIONS (PREVIOUSLY PEDIATRIC/HUMAN SUBJECTS)

5.1. Introduction

NIH sponsored clinical trials and the Code of Federal Regulations state that study participants enrolled in clinical trials must include women, ethnic minorities and children (individuals under the age of 21) to facilitate potential benefit to all persons at risk for a particular disease, disorder or condition under investigation unless there are scientific and/or ethical reasons for exclusion (*for more information, please refer to the BMT CTN Administrative Manual of Procedures, Chapter 7; Human Subjects Protection and Regulatory Procedures*).

Protocol Teams for studies having a large pediatric component and/or address important pediatric issues include members with appropriate pediatric expertise. When differences from adult care are important, appropriate care for a pediatric patient is clearly outlined within the protocol.

5.2. Purpose

The purpose of the Special Populations Committee is to ensure that women, children and ethnic minority study participants are considered for inclusion in all BMT CTN investigational protocols, including those involving non-malignant marrow disorders.

5.3. Membership

This committee consists of transplant physicians, the majority of whom have expertise in the transplantation of a pediatric population. There are several adult transplant physicians who serve as well. An NHLBI and a DCC statistician serve along with the DCC PI and a DCC co-PI in ex-officio capacity.

Non-ex-officio members serve for three year terms that are staggered to permit annual rotations.

5.4. Policy

This Standing Technical Committee is one of the four technical committees that review all final draft protocols at the time of submission to the Protocol Review Committee (PRC).

The Committee ensures that, for studies involving pediatric participants, appropriate modifications are addressed in the informed consent, patient care and monitoring documents. These differences must be appropriately addressed within the protocol, including off-label use of drugs for children.

Accrual of women, children and ethnic minorities is monitored by the DCC to determine whether their rates of enrollment are reflective of the distribution of potentially eligible patients expected from data reported to the Center for International Blood and Marrow Transplant Research (CIBMTR) and from published data related to the topic at hand. The DCC conducts this review periodically and reports results to the Data and Safety Monitoring Board (DSMB).

Procedure: *Ensures that women, children and ethnic minority study participants are considered for inclusion in protocols*

In general, all proposals and protocols shall include women, children and ethnic minority study participants. Should the exclusion of any of these patients be considered necessary, this must be clearly stated within the protocol and supported by appropriate evidence. Special attention is given by this committee to studies in which women, children or ethnic minority participants are excluded. Every effort is made by Protocol Teams to find solutions to possible exclusions so as to allow women, children and ethnic minorities onto BMT CTN trials. This may include the addition of a pediatric specialist on to the Protocol Team, or an alternative study design.

Examples of reasons to exclude these patients might include:

- Pediatric patients fall significantly outside the normal age range of a disease entity to suggest that inclusion of pediatric patients could introduce a significantly different biology of the disease/complication.
- No phase I testing of an experimental drug has previously been performed in children.
- The low incidence of a complication or rarity of a disease entity in the pediatric population could significantly underpower a study should a disproportionate or unexpectedly large number of children be enrolled.
- The protocol involves interviews of patients (and parents or guardians cannot serve as surrogates) and patient cooperation must be ensured.
- The disease or condition under study is unique to, or is relatively rare in women or one or more racial and/or ethnic minority population.
- The information on the difference in adverse outcomes or risk profiles for pregnant women is unknown.

Every effort is made to reconcile differences to the satisfaction of the Protocol Team and Special Populations Committee. If differences can not be resolved, the issue(s) is/are sent to the BMT CTN Executive Committee for adjudication.

6. PHARMACY

6.1. Introduction

It is anticipated that every BMT CTN protocol will employ pharmaceutical agents. In some protocols, these agents and their use in combination with other agents are established in the hematopoietic cell transplantation (HCT) setting and, therefore, will not require significant input from the Pharmacy Technical Committee. In other protocols, the agents will be investigational or approved for indications other than HCT.

6.2. Purpose

The purpose of the Pharmacy Standing Technical Committee is to assure that proper precautions and considerations are employed to decrease the likelihood of adverse events or other unintended consequences from use of both approved and investigational agents in BMT CTN studies and to optimize the acquisition of new knowledge regarding pharmaceutical agents used in the HCT setting.

6.3. Membership

This committee consists of transplant physicians, one of whom serves as Chair, and pharmacists from Core and Affiliate Centers. Two DCC staff members serve as ex-officio members. Non-ex-officio members serve for three year terms that are staggered to permit annual rotations.

6.4. Policy

This Standing Technical Committee is one of the four technical committees that reviews all final draft protocols at the time of submission to the Protocol Review Committee (PRC).

The Pharmacy Technical Committee will: 1) review all BMT CTN protocols for proper description, use, administration, and risks of pharmaceuticals; 2) assist in selection of a Central Pharmacy, when needed; and, 3) advise Protocol Teams on possible ancillary studies (e.g. pharmacokinetics that will enhance our knowledge about use and actions of drugs in the HCT setting).

Procedure: *Review Protocols for Proper Description, Use and Administration of Pharmaceuticals*

The primary purpose of the Committee is to critically review BMT CTN protocols for the use of all pharmaceutical agents including biologicals such as monoclonal antibodies and hematopoietic growth factors. This review will include details of formulation, administration, dose, and schedule. It will also include review for possible drug interactions. Descriptions of potential toxicities and adverse reactions of each pharmaceutical listed in the protocols will be reviewed for completeness and accuracy. In the case of investigational agents, the Committee will provide advice for monitoring usage, adverse events and data collection.

Procedure: *Assist in Selection of Central Pharmacy*

For certain protocols, pharmaceuticals may be purchased or acquired by the BMT CTN for distribution from a central pharmacy. Members of this Committee may review applications from

potential Central Pharmacy vendors and provide advice and oversight during the selection process. The review will include an assessment of blinding strategy (if applicable), storage and distribution plans and regulatory compliance.

Procedure: *Make Recommendations for Ancillary Studies*

The Committee will review protocols in development for considerations of important ancillary studies including pharmacokinetic analyses that might be of value. The Committee's input may include development of procedures for sample collection, assay procedures, reporting of results and recommended dosage adjustments. Potential ancillary study concepts will be communicated to the relevant Protocol Team for their consideration.

7. TOXICITY AND SUPPORTIVE CARE

7.1. Introduction

Organ toxicities can be, and often are, major complications following HCT. Because all or most study participants in BMT CTN trials will be receiving potentially toxic preparative therapy, significant regimen-related toxicity is anticipated (e.g., expected adverse events). In addition to providing guidance on standards of supportive care, this chapter also provides the evaluation and reporting procedures to be used for toxicities and adverse events (AEs) after HCT.

7.2. Purpose

The purpose of this Committee is to:

- Define methods for evaluation of AEs and toxicities after HCT;
- Review the evaluation and toxicity monitoring requirements for BMT CTN protocols;
- Review forms and procedures for collecting toxicity data, including standards for expedited reporting of certain AEs;
- Provide consensus guidelines for reporting toxicities; and,
- Describe appropriate procedures of supportive care.

The Committee provides advice to Protocol Teams regarding the frequency and detail of toxicity reporting that would be appropriate for each specific protocol.

7.3. Membership

This committee consists of transplant physicians. The DCC PI and a DCC co-PI serve as ex-officio members. Non-ex-officio members serve for three year terms that are staggered to permit annual rotations.

7.4. Policy

This Standing Technical Committee is one of the four technical committees that review all final draft protocols at the time of submission to the Protocol Review Committee (PRC).

The amount of information regarding toxicities to be monitored and collected varies by protocol. A protocol specific BMT CTN *toxicity data collection form* is designed for each protocol though these follow a Network standardized format; supportive care guidelines, also protocol specific, are included in each protocol. Individual Protocol Teams determine the extent to which variations in clinical standards of care are permitted for treatment and prevention of specific toxicities. If there are concerns regarding the effect of standard of care variations on primary or secondary protocol endpoints, the Toxicity and Supportive Care Committee assists the Protocol Team by providing recommendations for the standardization of such practices.

Procedure: *Define methods for evaluation of AEs and toxicities after HCT*

Expected toxicities and AEs are assessed at predetermined calendar endpoints (e.g. day 30, day 100 post HCT, etc.) and are defined by the Protocol Team in each protocol.

Wherever possible, investigators are encouraged to report AEs as syndromes or diseases rather than the individual symptoms and/or laboratory data. For example, pneumonitis should be reported as a single entity rather than as separate toxicities of tachypnea, rales, cough, hypoxia and pulmonary infiltrates.

Procedure: *Review the evaluation and toxicity monitoring requirements for BMT CTN protocols*
Definitions of toxicity generally follow *Common Terminology Criteria for Adverse Events* (CTCAE) criteria. Version 4.03 was incorporated into data collection tools (BMT CTN *Core Toxicity Forms*) moving forward for all studies beginning with BMT CTN 0901; prior to BMT CTN 0901, CTCAE version 3.0 was used.

All BMT CTN protocols include a protocol-specific list of toxicities that are routinely monitored and reviewed by a NHLBI Data and Safety Monitoring Board (DSMB). The level of detail and period of follow-up in reporting AE data is calibrated to the severity of the AE.

Procedure: *Review forms and procedures for collecting toxicity data, including standards for expedited reporting of certain AEs*

Expedited reports are filed with the DCC for grades 3-5 unexpected adverse events. These are reported by clinical sites via a web-based Adverse Event system. The Adverse Event Coordinator, a member of the DCC, reviews this system daily and forwards related information to the appropriate Medical Monitor for review.

The NHLBI Project Officer is notified of Grades 3-5 unexpected AEs, or concerns regarding the frequency or type of AE, by the DCC.

More information regarding expedited reports is detailed in Administrative MOP, Chapter 6 (*Adverse Event Reporting*).

8. CLINICAL RESEARCH ASSOCIATES

8.1. Introduction

Accurate and complete submission of data and related biologic samples are critical to the mission of the BMT CTN. Every attempt is made to maintain good channels of communication with center data managers/coordinators who are responsible for these activities. Clinical Research Associates (CRA) from across the Network are selected to provide input and put forth recommendations to the BMT CTN in the design of forms, protocols and policies related to data collection.

8.2. Purpose

The purpose of the CRA Standing Technical Committee is to assure that data collection and logistical issues, from the viewpoint of a CRA or Data Manager, are considered in protocol development, data and sample collection, educational materials and protocol implementation.

8.3. Membership

This committee consists of CRAs and Data Managers from Core and Affiliate Centers. A DCC representative who serves as Chair coordinates monthly conference calls/meetings. He/she is appointed by a DCC co-PI who is present during most meetings. Other DCC or NIH staff serve as ex officio members. Non-ex-officio members serve for three year terms that are staggered to permit annual rotations.

Members of the CRA Technical Committee serve on the BMT CTN Coordinators' Meeting Planning Committee to guarantee relevant topics are being addressed such as Adverse Event (AE) reporting, data collection forms and accrual initiatives.

8.4. Policy

This Standing Technical Committee is one of the four technical committees that review all final draft protocols at the time of submission to the Protocol Review Committee (PRC).

The CRA Technical Committee will assist in the development of Case Report Forms (CRFs) and data collection systems for specific protocols; review and help resolve logistical issues in protocol implementation (e.g., issues related to shipping and receipt of specimens or drugs); and, review educational materials for use at participating clinical centers.

Procedure: *Reviews new protocols prior to finalization*

This committee reviews all protocols from a CRA perspective. Members review the entire protocol focusing on treatment plans, required observations and the informed consent. This ensures that the protocol is accurate, reasonable and feasible. The relevant Protocol Coordinator functions as liaison between this committee and the Protocol Team. Every effort is made to reconcile differences to the satisfaction of the Protocol Team and CRA Technical Committee.

Procedure: *Assists in development of Case Report Forms (CRFs)*

This Technical Committee reviews the final draft protocol to assess whether existing data collection tools adequately capture data required to answer the primary question of the protocol or if a new, protocol-specific form is required. In the latter case, this committee helps develop the new form and assures that it is designed to meet data collection requirements of the protocol.

Procedure: *Helps resolve logistical issues in protocol implementation*

This committee addresses the logistics of issues such as shipping details, receipt of drugs, handling of biologic sampling, etc. It ensures that practices are standardized and that instructions are clearly stated and are practical enough to avoid problems at the transplant centers.

Procedure: *Ensures that educational materials for use at clinical centers are appropriate and are readily available*

Certain protocols require that the DCC prepare educational materials for use at the clinical site. This committee assures that these materials are practical and understandable for patient and/or staff use.

APPENDIX 2-A

CHRONIC GVHD

I. Objectives of the NIH Consensus Project

- Develop definitions and tools for conducting clinical trials in chronic GVHD
- Outline current standards of clinical care
- Identify critical directions for future basic and clinical research

II. Background

Chronic graft-versus-host disease (GVHD) is one of the most devastating long-term complications after infusion of allogeneic hematopoietic stem cells and it remains one of the major barriers to successful transplantation. About 7000 patients (6000 with cancer) are treated each year in North America by allogeneic stem cell transplantation (alloSCT) and chronic GVHD is reported in about 50%. Chronic GVHD treatment is clinically challenging with little progress in therapy in the last twenty years. The survival rate after diagnosis of chronic GVHD has barely improved despite advances in supportive care. In addition, chronic GVHD is associated with decreased quality of life, impaired functional status, and continued need for immunosuppressive medications.

Barriers to the conduct of studies in chronic GVHD include: (a) poor understanding of biology of the disease; (b) methodological challenges, including absence of criteria for clinical trials; (c) logistical challenges, including a relatively small potentially eligible population; and, (d) limited understanding of the clinical syndrome in the modern era of transplantation technology. Better clinical research tools are needed so that the impact of novel agents on the development and course of chronic GVHD can be appropriately and timely assessed.

Recognizing the above issues the NIH convened in June 2004 a consensus conference-planning meeting with the goal of advancing research in chronic GVHD and fostering difficult interdisciplinary research. The uniqueness of this effort is the joint initiative of both intramural and extramural branches of the NIH (NCI, NHLBI, NIAID) as well as other government agencies such as ORD, HRSA and DD, with active representation of FDA. Six working groups were formed and charged to develop a priority list of issues to be addressed and propose a course of action based on broad input of all stakeholders. In a series of conference calls using a consensus process approach, groups have prepared documents covering pathologic classification, diagnosis and staging, response criteria, biomarkers, clinical trials, and supportive care.

On November 16 and 17, 2004 a face-to-face conference was held in Bethesda, Maryland that included about 80 participants from the USA, and with active participation of the stem cell transplant organizations from Canada and Europe. A draft summary of the recommendations and future directions was prepared by each of the six working groups to serve as a template for broader consensus building and discussions. This phase of process was presented in an open chronic GVHD conference on June 6, 2005 in Bethesda. It included a broad representation of stem cell transplant clinicians, industry, academia, patients and regulatory agencies. The June

conference will produce a summary position guideline on future chronic GVHD research and a series of educational Consensus documents which will be published over the next year and will serve as models to begin prospective testing of these Consensus principles. This process is expected to accelerate and facilitate the conduct and funding of chronic GVHD clinical trials.

APPENDIX 2-B

DRAFT GRID FOR CHRONIC GVHD SEVERITY SCORING

Clinician Assessment Form – Current visit

Date: _____ **Subject ID:** _____

	0	1	2	3
Skin	<input type="checkbox"/> No changes	<input type="checkbox"/> < 18% BSA lichenoid, sclerodermatous, or ichthyotic involvement <input type="checkbox"/> Eczema hypo or hyperpigmentation	<input type="checkbox"/> 18-50% BSA lichenoid, sclerodermatous, or ichthyotic involvement	<input type="checkbox"/> > 50% BSA involved <input type="checkbox"/> Interference with ADLs due to impaired mobility <input type="checkbox"/> Skin ulcerations
Hair Loss	<input type="checkbox"/> None	<input type="checkbox"/> Mile (<50%)	<input type="checkbox"/> >50%	
Joints	<input type="checkbox"/> No contractures <input type="checkbox"/> Arthralgias <input type="checkbox"/> Migratory arthritis	<input type="checkbox"/> Persistent arthritis in 1-2 joints	<input type="checkbox"/> Mild joint contractures (do not affect ADL) <input type="checkbox"/> Polyarticular arthritis	<input type="checkbox"/> Severe joint contractures (interfere with ADLs)
Oral	<input type="checkbox"/> No changes	<input type="checkbox"/> Symptomatic but no change in diet	<input type="checkbox"/> Able to eat most foods, although some dietary changes due to oral chronic GVHD	<input type="checkbox"/> Unable to eat most foods due to oral chronic GVHD
Ocular	<input type="checkbox"/> No changes	<input type="checkbox"/> Dry eyes but not requiring therapy <input type="checkbox"/> Keratoconjunctivitis, asymptomatic	<input type="checkbox"/> Dryness of eyes requiring artificial tears, lacrimal plugging, or Schirmer's < 5 mm <input type="checkbox"/> Keratoconjunctivitis, symptomatic	<input type="checkbox"/> Pseudomembranes <input type="checkbox"/> Corneal ulcerations <input type="checkbox"/> Loss of vision
Esophagus	<input type="checkbox"/> No changes	<input type="checkbox"/> Symptomatic but can eat regular diet	<input type="checkbox"/> Dysphagia or odynophagia requiring dietary changes	<input type="checkbox"/> Need for parenteral nutrition <input type="checkbox"/> Web/stricture formation
Pulmonary	<input type="checkbox"/> Asymptomatic	<input type="checkbox"/> 75-90% FEV1/FVC <input type="checkbox"/> Asthma	<input type="checkbox"/> Dyspnea with exertion <input type="checkbox"/> 50-74% FEV1/FVC <input type="checkbox"/> Desaturation with exercise	<input type="checkbox"/> Dyspnea with normal activities <input type="checkbox"/> < 50% FEV1/FVC <input type="checkbox"/> Requires supplemental oxygen
KPS	<input type="checkbox"/> Asymptomatic and fully active (ECOG 0, KPS 100%) <input type="checkbox"/> Lansky = 90-100%	<input type="checkbox"/> Symptomatic; fully ambulatory; restricted in physically strenuous activity (ECOG 1, KPS 80-90%) <input type="checkbox"/> Lansky = 70-80%	<input type="checkbox"/> Symptomatic; ambulatory, capable of self-care, > 50% of waking hours are spent out of bed (ECOG 2, KPS 60-70%) <input type="checkbox"/> Lansky = 50-60%	<input type="checkbox"/> Symptomatic; limited self care, spends > 50% of waking hours in bed but, not bedridden (ECOG 3, KPS 40-50%) <input type="checkbox"/> Lansky = <50%

APPENDIX 2-B

DRAFT GRID FOR CHRONIC GVHD SEVERITY SCORING

Clinician Assessment Form – Current visit

Date: _____ **Subject ID:** _____

	0	1	2	3
GI Manifestations	<input type="checkbox"/> None	<input type="checkbox"/> Anorexia or malabsorption ± <5% weight loss or, in children, growth deviation of <5% of pre-transplant percentile after 1 year post transplant	<input type="checkbox"/> Anorexia or malabsorption ± 5-10% weight loss or, in children, growth deviation of <5% of pre-transplant percentile after 1 year post transplant	<input type="checkbox"/> Anorexia or malabsorption ± >20% weight loss or, in children, growth deviation of <5% of pre-transplant percentile after 1 year post transplant
Hematologic	<input type="checkbox"/> Thrombocytopenia not attributable to other causes >100K	<input type="checkbox"/> Thrombocytopenia not attributable to other causes >75K	<input type="checkbox"/> Thrombocytopenia not attributable to other causes >50K	<input type="checkbox"/> Thrombocytopenia not attributable to other causes <50K
Autoimmune (e.g., IPT, AHA)	<input type="checkbox"/> None	<input type="checkbox"/> Positive laboratory tests, clinically not requiring treatment	<input type="checkbox"/> Requires <6 months additional immunosuppressive therapy to control symptoms	<input type="checkbox"/> Requires transfusions (AHA) or splenectomy (ITP) or >6 months of increased immunosuppression to control disease
Laboratory and clinical variables (Please complete for this visit date)	Platelets _____ x 10 ⁹ /L Total bilirubin _____ mg/dl Alkaline phosphatase _____ mg/dl Weight _____ kg or lb (circle unit of measure)			
Specific manifestations (Please circle Yes, No, or Not applicable)	Serositis Y / N Scleroderma Y / N Myositis Y / N Steatorrhea Y / N Fasciitis Y / N Vaginitis/vaginal stricture Y / N / NA			

Initials of person completing this form: _____

APPENDIX 2-C

CHRONIC GVHD CODE BOOK

Mild: signs and symptoms of chronic GVHD do not interfere substantially with function and do not progress once appropriately treated with local therapy or standard systemic therapy (steroids and/or cyclosporine or tacrolimus).

Moderate: signs and symptoms of chronic GVHD interfere somewhat with function despite appropriate therapy or are progressive through first line systemic therapy defined as steroids and/or cyclosporine or tacrolimus.

Severe: signs and symptoms of chronic GVHD limits function substantially despite appropriate therapy or are progressive through second line therapy.

APPENDIX 2-D
CHRONIC GVHD AUDITING TOOL

(Under Development)

APPENDIX 4-A

SEVERITY GRADING TABLE AND
RECURRENCE INTERVAL DEFINITIONS

Type of Infection/ Severity Grade	Grade 1	Grade 2	Grade 3
Bacterial infections	<p>Bacterial focus NOS requiring no more than 14 days of therapy for treatment (e.g urinary tract infection)</p> <p>Coag Neg Staph (S. epi), Corynebacterium, or Propriobacterium bacteremia</p> <p>Cellulitis responding to initial therapy within 14 days</p> <p>C. Difficile toxin positive stool with diarrhea < 1L without abdominal pain (child < 20 mL/kg)</p>	<p>Bacteremia (except CoNS) without severe sepsis ***</p> <p>Bacterial focus with persistent signs, symptoms or persistent positive cultures requiring greater than 14 days of therapy</p> <p>Cellulitis requiring a change in therapy d/t progression Localized or diffuse infections requiring incision with or without drain placement</p> <p>Any pneumonia documented or presumed to be bacterial</p> <p>C. Difficile toxin positive stool with diarrhea ≥ 1L (child ≥ 20 mL/kg) or with abdominal pain</p>	<p>Bacteremia with deep organ involvement (e.g. with new or worsening pulmonary infiltrates; endocarditis)</p> <p>Severe sepsis with bacteremia.</p> <p>Fasciitis requiring debridement</p> <p>Pneumonia requiring intubation</p> <p>Brain abscess or meningitis without bacteremia</p> <p>C. Difficile toxin positive stool with toxic dilatation or renal insufficiency with/without diarrhea</p>
Fungal infections	<p>Superficial candida infection (e.g. oral thrush, vaginal candidiasis)</p>	<p>Candida esophagitis (biopsy proven).</p> <p>Proven or probable fungal sinusitis confirmed radiologically without orbital, brain or bone involvement.</p>	<p>Fungemia including Candidemia</p> <p>Proven or probable invasive fungal infections (e.g., Aspergillus, Mucor, Fusarium, Scedosporium).</p>

Type of Infection/ Severity Grade	Grade 1	Grade 2	Grade 3
Fungal infections continued			Disseminated infections (defined as multifocal pneumonia, presence of urinary or blood antigen, and/or CNS involvement) with Histoplasmosis, Blastomycosis, Coccidiomycosis, or Cryptococcus. <i>Pneumocystis jiroveci</i> pneumonia (regardless of PaO2 level)
Viral infections	Mucous HSV infection Dermatomal Zoster Asymptomatic CMV viremia untreated or a CMV viremia with viral load decline by at least 2/3 of the baseline value after 2 weeks of therapy EBV reactivation not treated with rituximab Adenoviral conjunctivitis asymptomatic viruria, asymptomatic stool shedding and viremia not requiring treatment Asymptomatic HHV-6 viremia untreated or an HHV-6 viremia with a viral load decline by at least 0.5 log after 2 weeks of therapy BK viremia or viruria with cystitis not requiring intervention	VZV infection with 3 or more dermatomes Clinically active CMV infection (e.g. symptoms, cytopenias) or CMV Viremia not decreasing by at least 2/3 of the baseline value after 2 weeks of therapy EBV reactivation requiring institution of therapy with rituximab Adenoviral upper respiratory infection, viremia, or symptomatic viruria requiring treatment Clinically active HHV-6 infection (e.g. symptoms, cytopenias) or HHV-6 viremia without viral load decline 0.5 log after 2 weeks of therapy BK viremia or viruria with clinical consequence requiring prolonged therapy and/or surgical intervention	Severe VZV infection (coagulopathy or organ involvement) CMV end-organ involvement (pneumonitis, enteritis, retinitis) EBV PTLD Adenovirus with end-organ involvement (except conjunctivitis and upper respiratory tract)

Type of Infection/ Severity Grade	Grade 1	Grade 2	Grade 3
Viral infections continued	Viremia (virus not otherwise specified) not requiring therapy	Enterocolitis with enteric viruses Symptomatic upper tract respiratory virus Any viremia (virus not otherwise specified) requiring therapy	Lower tract respiratory viruses Any viral encephalitis or meningitis
Parasitic infections			CNS or other organ toxoplasmosis Strongyloides hyperinfection
Nonmicrobiologically defined infections	Uncomplicated fever with negative cultures responding within 14 days Clinically documented infection not requiring inpatient management	Pneumonia or bronchopneumonia not requiring mechanical ventilation Typhlitis	Any acute pneumonia requiring mechanical ventilation Severe sepsis*** without an identified organism

*Concomitant or multimicrobial infections are graded according to the grade of the infection with the higher grade of severity.

**Therapy includes both PO and IV formulations

***Severe Sepsis:

Adults:

Hypotension

-A systolic blood pressure of <90 mm Hg or a reduction of >40 mm hg from baseline in the absence of other causes for hypotension

Multiple Organ Dysfunction Syndrome

-2 or more of the following: Renal failure requiring dialysis, respiratory failure requiring bipap or intubation, heart failure requiring pressors, liver failure

Pediatrics:

- Pediatric SIRS definition and suspected or proven infection and cardiovascular dysfunction or ARDS or TWO or MORE other organ dysfunctions

Pediatric SIRS definition:

Two or more of the following, ***one of which must be abnormal temperature or leukocyte count***

- 1) Core temperature $>38.5\text{C}$ ***or*** $< 36\text{C}$
- 2) Tachycardia, otherwise unexplained persistent in absence of external stimulus, chronic drugs or painful stimuli. ***or*** bradycardia, in < 1 year old, otherwise unexplained persistent.
- 3) Tachypnea or mechanical ventilation for an acute process not related to underlying neuromuscular disease or general anesthesia
- 4) Leukocytosis or leukopenia for age (not secondary to chemotherapy) or $>10\%$ bands

Pediatric organ dysfunction criteria:

Cardiovascular: despite administration of fluid bolus ≥ 40 ml/kg in 1 hour:

- Hypotension $< 5^{\text{th}}$ percentile for age (***or*** per Table 1)
- Pressors at any dose
- Two of the following:
 - Capillary refill > 5 secs
 - Core to peripheral temperature gap $> 3^{\circ}\text{C}$
 - Urine output < 0.5 mL/kg/hr
 - Unexplained metabolic acidosis (Base deficit > 5.0 mEq/L)
 - Blood lactate > 2 x ULN

Respiratory:

- ARDS ***or***
- Intubated ***or***
- $>50\%$ FiO₂ to maintain SaO₂ $> 92\%$

Neurological:

- Glasgow Coma Score ≤ 11 ***or***
- Acute change in mental status with a decrease in GSC ≥ 3 pts from abnormal baseline

Renal:

- Serum creatinine ≥ 2 x ULN for age ***or*** 2-fold increase in baseline creatinine

Hepatic:

- Total bilirubin ≥ 4 mg/dL ***or***
- ALT ≥ 2 x ULN for age

TABLE 1: FOUR AGE GROUPS RELEVANT TO HCT:

Age	Tachycardia (bpm)	Bradycardia (bpm)	Tachypnea (breaths/min)	Leukocytosis / Leukopenia (WBC)	Hypotension Systolic BP mmHg
1 mo to 1 yr	>180	<90	>34	>17.5 to <5.0	<100
2 yr to 5 yr	>140	NA	>22	>15.5 to <6.0	<94
6 yr to 12 yr	>130	NA	>18	>13.5 to <4.5	<105
13 yr to < 18 yr	>110	NA	>14	>11 to <4.5	<117

Disseminated Infections:

1. Two or more non-contiguous sites with the SAME organism
2. A disseminated infection can occur at any level of severity, but most will be grade 2 or 3.

Recurrence Intervals to Determine Whether an Infection is the Same or New:

1. CMV, HSV, EBV, HHV6: 2 months (< 60 days)
2. VZV, HZV: 2 weeks (< 14 days)
3. Bacterial, non-C. difficile: 1 week (< 7 days)
4. Bacterial, C. difficile: 1 month (< 30 days)
5. Yeast: 2 weeks (< 14 days)
6. Molds: 3 months (< 90 days)
7. Helicobacter: 1 year (< 365 days)
8. Adenovirus, Enterovirus, Influenza, RSV, Parainfluenza, Rhinovirus: 2 weeks (< 14 days)
9. Polyomavirus (BK virus): 2 months (< 60 days)

For infections coded as “Disseminated” per the *Infection Form*, any previous infection with the same organism but different site within the recurrence interval for that organism will be counted as part of the disseminated infection.